Nutrition, Metabolism & Cardiovascular Diseases (2015) **25**, 236–241

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Serum fructosamine and risk of cardiovascular and all-cause mortality: A 24-year prospective population-based study

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Received 16 July 2014; received in revised form 1 September 2014; accepted 23 September 2014
Available online 5 October 2014

KEYWORDS
Fructosamine;
Cardiovascular mortality;
All-cause mortality;
Risk factor;
Prospective study

Abstract *Background and aims:* The association between fructosamine and cardiovascular complications is not well established. We sought to evaluate whether serum fructosamine may be a risk factor for cardiovascular and all-cause mortality in nondiabetic subjects.
Methods and results: Fructosamine and other cardiovascular risk factors were measured in a sample of 1909 nondiabetic middle-aged men without a known history of coronary heart disease (CHD) at baseline. Associations between baseline fructosamine levels and fatal CHD and cardiovascular disease (CVD) events, and all-cause mortality were estimated using a Cox regression analysis, progressively adjusted for potential confounders. Mean baseline age was 52 years and 30% were smokers. During a median follow-up of 24 years (interquartile range: 18–26 years), 177 (9%) fatal CHD, 289 (15%) fatal CVD, and 728 (38%) all-cause mortality events occurred. In analyses adjusted for several conventional risk factors (i.e., age, systolic blood pressure, smoking, LDL- and HDL-cholesterol), the hazard ratios (HRs) comparing top vs bottom quartile of serum fructosamine levels resulted: 1.33 (95% CI: 0.97, 1.82; $p = 0.078$) for CHD death and 0.93 (0.72, 1.19; $p = 0.567$) for CVD death, and 1.04 (0.89, 1.22; $p = 0.617$) for all-cause mortality. In similar comparisons, further adjustments for body mass index, alcohol consumption, C-reactive protein, and fasting plasma glucose did not materially change these estimates. The exclusion of participants with prevalent CVD at baseline yielded similar results.
Conclusion: In our cohort of nondiabetic men without known CHD, baseline fructosamine levels were not independently associated with cardiovascular and all-cause mortality. Further studies are warranted to confirm these results in other populations.

Introduction

Serum fructosamine is a glycoprotein formed via a nonenzymatic mechanism that involves the binding of plasma glucose to serum proteins to form ketoamines [1] and, along with glycated hemoglobin (HbA1c), is commonly used to assess glucose control in subjects with diabetes. However, compared to HbA1c, fructosamine has a shorter half-life and reflects the physiology of glucose metabolism in the extracellular space, whereas HbA1c indicates glycosylation process in the intraerythrocyte

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment – insulin resistance; HR, hazard ratio; LDL, low-density lipoprotein; $\log_e$, natural logarithm; SBP, systolic blood pressure; SD, standard deviation.

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http://dx.doi.org/10.1016/j.numecd.2014.09.007
0939-4753/

compartment [1]; therefore, fructosamine provides information on blood glucose over the previous 2–4 weeks (compared to 12–16 for HbA1c) and when the interpretation of HbA1c is confounded by the presence of some underlying conditions such anemic states, hemoglobinopathies, and renal diseases [2].

Previous prospective studies have investigated the relationship between HbA1c and various outcomes in nondiabetic subjects, showing that higher HbA1c levels are related to an increased risk of incident vascular and nonvascular events [3–6]. On the other hand, it is still unclear whether fructosamine is associated with the risk of cardiovascular disease in the general population (i.e. participants not selected on the basis of having previous diseases) [7]. A cross-sectional [8] and a case-cohort study [9] have suggested an association between fructosamine levels and macro- and microvascular complications. More recently, fructosamine has also been associated with all-cause and cardiovascular disease mortality and morbidity in a prospective study of hemodialysis patients [10], as well as with the risk of retinopathy in a cohort analysis of diabetic and nondiabetic subjects [11].

However, to our knowledge, no prospective study has assessed the relationship between fructosamine and cardiovascular disease in the general population. Therefore, the objective of this study was to evaluate the relationship between serum fructosamine and cardiovascular and all-cause mortality in a prospective cohort of middle-age nondiabetic men.

Methods

This study was performed following the STROBE guidelines for observational studies in epidemiology [12].

Study population

The design of the Kuopio Ischaemic Heart Disease (KIHD) Risk Factor Study has been published in detail previously [13]. The study was initially planned to investigate risk predictors for atherosclerotic cardiovascular outcomes in a population-based sample of men from Eastern Finland, and subsequently extended to women (Supplementary Fig. S1; www.uef.fi/fi/nutritionepidemiologists/kihd).

This analysis included only male participants. At baseline (March 1984–December 1989), the study population was a random sample of men living in the city of Kuopio or neighboring rural communities, stratified and balanced into 4 age-groups: 42, 48, 54, or 60 years old, and selected from population registries of all inhabitants living in the area; of those who were invited, 2682 (83%) participated in the study. Men with prevalent diabetes (either having regular treatment with an oral hypoglycemic agent, insulin therapy, or having treatment only with diet while also having a fasting plasma glucose (FPG) level of at least 7.0 mmol/L according to the 2014 American Diabetes Association criteria [14]; $N = 162$) and prevalent coronary heart disease (CHD, defined as history of myocardial infarction or stable/unstable angina; $N = 611$) were excluded; therefore, 1909 participants remained for the analysis. The study was approved by the Research Ethics Committee of the University of Eastern Finland and each participant gave written informed consent.

Assessment of risk factors

Blood samples were taken between 8 and 10am. In addition to fasting, they were instructed to abstain from drinking alcohol for at least 3 days prior and from smoking for at least 12 h. A 30-min rest period was allowed in the supine position before blood collection using vacuum tubes (Terumo Venoject; Terumo, Tokyo, Japan). No tourniquet was used during the blood collection.

The measurements of serum fructosamine and albumin concentrations were made in 1991 from frozen serum samples photometrically (Boehringer Mannheim, Mannheim, Germany) by a colorimetric method in an autoanalyzer (Kone Specific, Kone inc, Espoo, Finland). Blood hemoglobin was measured photometrically (Gliford Stsar III, Instrument Laboratories Inc.) using the cyanmethemoglobin method. Serum insulin level was determined using a radioimmunoassay kit (Novo Biolabs; Novo Nordisk, Bagsvaerd, Denmark). The serum samples were stored frozen at −80 °C for 0.2–2.5 years. The between batch coefficient of variation was 8.9% for 65 pmol/L and 17.5% at 222 pmol/L ($n = 10$). The values obtained were immunoreactive insulin as the assay has cross reactivity with proinsulin. A glucose dehydrogenase method (Merck, Darmstadt, Germany) was used to assess the blood glucose after precipitation of proteins by trichloroacetic acid. Insulin resistance was estimated as follows: HOMA-IR = fasting plasma insulin (μU/mL) × FPG (mmol/L)/22.5. The cholesterol contents of lipoprotein fractions and serum triglycerides were measured enzymatically (Boehringer Mannheim, Mannheim Germany) on the day after the high-density lipoprotein was separated from fresh samples by ultracentrifugation and precipitation. Serum C-reactive protein (CRP) was measured with an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; DPC, Los Angeles, CA).

The resting systolic blood pressure (SBP) was measured between 8 and 10am with a random-zero sphygmomanometer (Hawksley, Lancing England) by two trained nurses using the following protocol: after supine rest of 5 min, 3 measurements in supine, 1 in standing and 2 in sitting position with 5-min intervals. The systolic blood pressure was taken as the mean of all 6 measurements [15]. Baseline diseases, smoking habits and years of education (from the age of seven year-old) were assessed by self-administered questionnaires. The diagnosis of chronic diseases was checked during a medical examination by the internist. Alcohol consumption (g/week) was assessed using the Nordic Alcohol Consumption Inventory [15]. Body mass index (BMI) was computed as the ratio of weight in kilograms to the square of height in meters.